Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Hilton Washington DC North/Gaithersburg 620 Perry Parkway, Gaithersburg, Maryland July 13 - 14, 2010

QUESTIONS TO THE COMMITTEE

- 1. Please discuss the strengths and weaknesses of the various sources of data available to address the question of risk of ischemic cardiovascular (CV) events (i.e., stroke and myocardial infarction) in patients treated with rosiglitazone:
 - a) in comparison to other non-thiazolidinedione (TZD) anti-diabetic agents (i.e., metformin, sulfonylureas)
 - b) in comparison to pioglitazone

In your discussion, please specifically consider and discuss the following:

- -similarities and differences of the patient populations
- -methods utilized to ensure complete and accurate ascertainment and adjudication of CV events
- -the potential for publication bias
- -study methodology
- -findings in subgroups
- -the consistency of the results
- 2. Considering the available data, do you find that rosiglitazone (choose 1):
 - A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
 - B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
 - C. I am not able to make a finding A or B.

Please discuss the rationale for your vote.

- 3. Considering the available data, do you find that rosiglitazone (choose 1):
 - A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
 - B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
 - C. I am not able to make a finding A or B.

Please discuss the rationale for your vote.

- 4. Please discuss the strengths and weaknesses of the various sources of data available to address the question of risk of mortality in patients treated with rosiglitazone:
 - a) in comparison to other non-TZD anti-diabetic agents (i.e., metformin, sulfonylureas)
 - b) in comparison to pioglitazone
- 5. Considering the available data, do you find that rosiglitazone (**choose 1**):
 - A. Increases the risk of mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
 - B. Does not increase the risk of mortality in patients with Type 2 diabetes relative to non-TZD antidiabetic agents.
 - C. I am not able to make a finding A or B.

Please discuss the rationale for your vote.

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- 6. Considering the available data, do you find that rosiglitazone (**choose 1**):
 - A. Increases the risk of mortality in patients with Type 2 diabetes relative to pioglitazone.
 - B. Does not increase the risk of mortality in patients with Type 2 diabetes relative to pioglitazone.
 - C. I am not able to make a finding A or B.

Please discuss the rationale for your vote.

- 7. Rosiglitazone and other oral anti-diabetic therapies share the same indication of improving glycemic control in patients with Type-2 diabetes. Based on the available data, please discuss the benefit-to-risk profile of rosiglitazone in the context of other available anti-diabetic therapies.
- 8. Based on the available data, which of the following regulatory actions do you recommend FDA pursue regarding rosiglitazone? **Please select only one option or if you wish to abstain, do not vote.** (These options are listed from most favorable to rosiglitazone to least favorable to rosiglitazone and do not reflect any prejudgment on the part of FDA.)
 - A. Allow continued marketing and revise the current label to remove the boxed warning and other warnings regarding an increased risk of ischemic CV events, or
 - B. Allow continued marketing and make no changes to the current label, or
 - C. Allow continued marketing and revise the current label to add additional warnings (e.g., contraindications for certain patient populations, recommendation for second-line use in patients intolerant of or uncontrolled on other anti-diabetic agents); or
 - D. Allow continued marketing, revise the current label to add additional warnings, <u>and</u> add additional restrictions on use (such as restricting prescribing to certain physicians or requiring special physician and patient education)
 - E. Withdrawal from the U.S. market.

Please explain the rationale for your vote.

9. If rosiglitazone remains on the U.S. market, do you recommend that the Thiazolidinedione Intervention With Vitamin D Evaluation (TIDE) trial be continued in order to provide further data on the comparative CV safety of rosiglitazone, pioglitazone, and standard-of-care management of type 2 diabetes (placebo add-on)?

Please vote <u>ves</u> or <u>no</u> and discuss the rationale for your vote. Please discuss any recommendations for changes to the TIDE protocol or informed consent.